Supporting Information

High Solubility Piperazine Salts of NSAID Meclofenamic Acid

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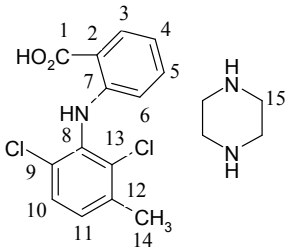
Table S1 Refcodes of cocrystals (20 hits) and salts (25 hits, marked with *) of piperazine (CSD database, November 2011 update).

BODHIM*	BIXXIQ*	CIQZUI*	COKCEL	CUBWUS	CUYXEA*
DIVCUH	DIVDOC	DOSJOK	DUVHOS*	ERUNOU	EXOKUX*
EWAQOJ	FEKQOC	HEVQEF*	HIBFED	HUSWUN*	JESMEA
KEQLIC*	KOWLIR*	KUFBIX*	KUZQOM*	LOHNOM	MOBYOR
MUPPZUI	OFETAU*	OGEZIJ	OWAVUE	PULWOI*	QAJNEW*
QAMRAY	QAQBUG*	QIBSID*	QIGCEO*	QIXREV*	RACNIS
RAWFAW	RUVNOM*	TICFOA	TUWNEV*	UHOXAR	VADTOK*
VAJWUZ*	VUZYUL*	XISREX*			

Table S2 Refcodes of piperazinium dications with carboxylate anions (73 hits**)** (CSD database, November 2011 update). Refcodes marked with * contain both mono and di piperazinium cations are present in the same crystal structure. One refcode (CUKVOU in bold) was contains piperazinium monocation.

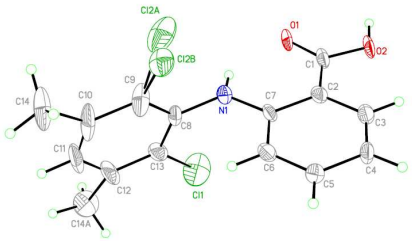
ALOQIC	ALOQOI	ALOQUO	ALORAV	APOKUM	APOLAT
BAGJIC10	BAGJOI	BAGKAV10	BAKYES	BAYCOT	BEXCEM10
BEXDAJ01	BEXDIR01	BIXXIQ	BOCLIO	BOQFES	BURWEQ
CUKVIO	**CUKVOU**	CUYXAW	CUYXEA	DATFIO	DUVHOS
EXEKEX	EXOKUX	FECVUF	FEFQOX	HEVQEF	HEZTAI
HIHJOX	HIRCAN	HUSWOH	IXAREE	KEQLIC	KOWLIR
KUFBET	KUFBIX	KUFBOD	KUFBUJ	KUZQOM	MABYIY
MELYIY	MOSSOD	MOXROH	NIFGIS	NIQMUW*	NUKWAS
OFETAU	OMUXUQ	PULWOI	QAJNEW	QAQBUG	QIBRUO
QIGCEO	QIXSEW	QOYHER	RIKBIW	RIKBOC	RIQHOP
RUVNOM	TEWXEY	VADTOK	VAJWUH	VABQOG	VUZYUL
XISREX	YEJMEF	YEQZAW	YIFMUW	ZUGQEX01	TUWNUV
UREZOH					

Table S3 ^{13}C solid-state NMR chemical shifts (δ, ppm) in piperazinium meclofenamate salts compared to values for the pure coformers. Atom numbering is shown below.

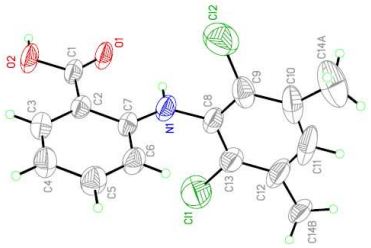


^{13}C peak atom #	MFA−PPZ-M	MFA−PPZ−H_2O	MFA−PPZ	MFA	PPZ
1	173.3	172.96	175.07, 173.82	174.70	---
2, 6	110.69	110.94	113.08	110.98	---
3, 12	126.45	127.06	129.98	128.62	---
4	114.84, 118.57	115.56	117.12, 116.47	115.58	---
5, 13	130.18	129.95	133.50	133.75	---
7	146.35	144.43	146.47, 145.18	147.46	---
8, 9	135.98	135.38	136.47	136.87, 137.32	---
10, 11	126.45	126.63	127.11	126.56, 127.33	---
14	18.79	18.43	21.23, 19.58	20.06, 18.34	---
15	41.87	41.74	40.95, 37.33	---	45.35

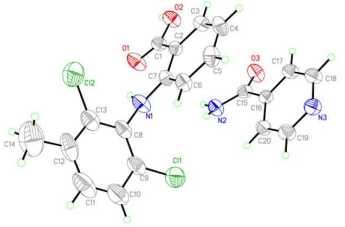
.



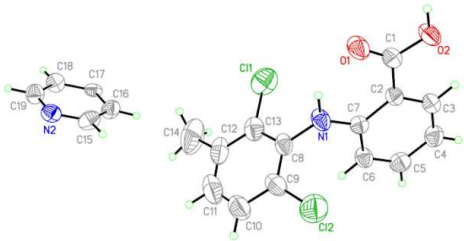
(a)



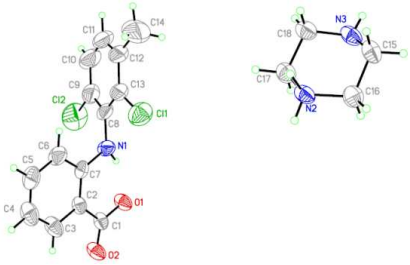
(b)



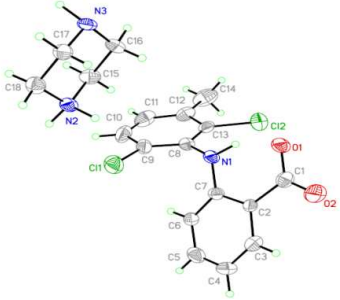
(c)



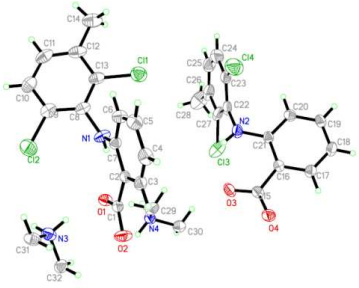
(d)



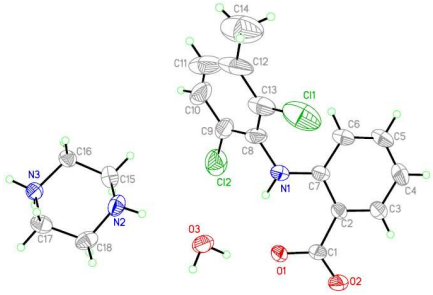
(e)



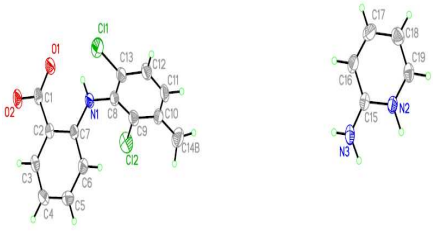
(f)



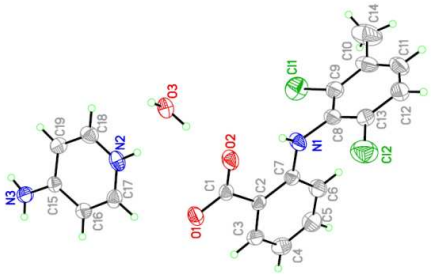
(g)



(h)

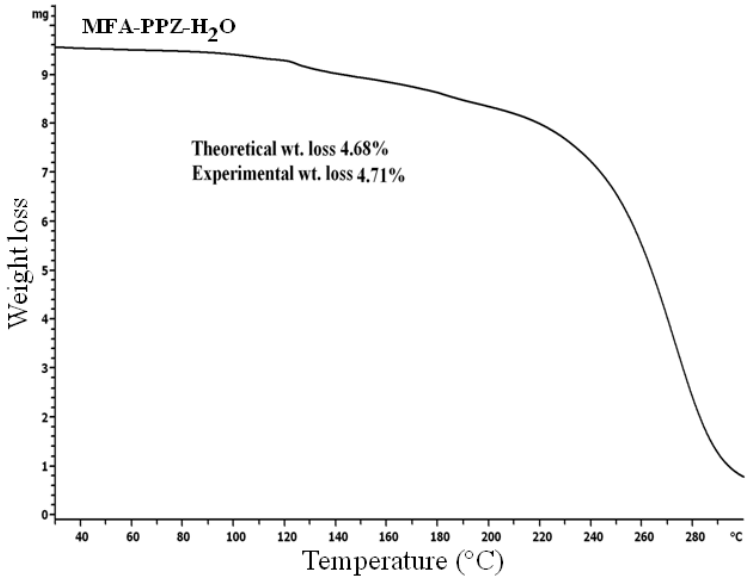


(i)

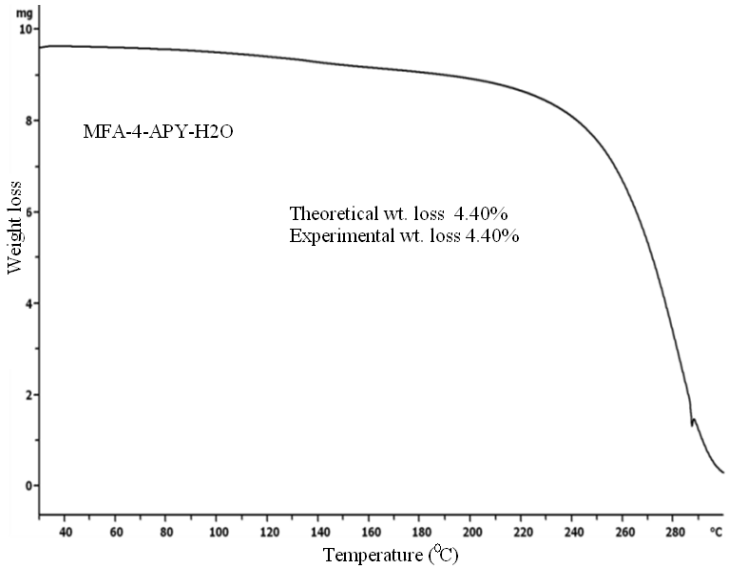


(j)

Figure S1 ORTEP diagrams of (a) MFA-100K, (b) MFA-RT (c) MFA–INA (1:1) cocrystal, (d) MFA–BPY (1:0.5) cocrystal, (e) MFA–PPZ-M (1:1) salt, (f) MFA–PPZ-O (1:1) salt, (g) MFA–PPZ (2:1) salt, (h) MFA–PPZ–H_2O (1:1:1) salt monohydrate, (i) MFA–2-APY (1:1) salt, and (j) MFA–4-APY–H_2O (1:1:1) salt hydrate at 35% probability of thermal ellipsoids for heavy atoms.

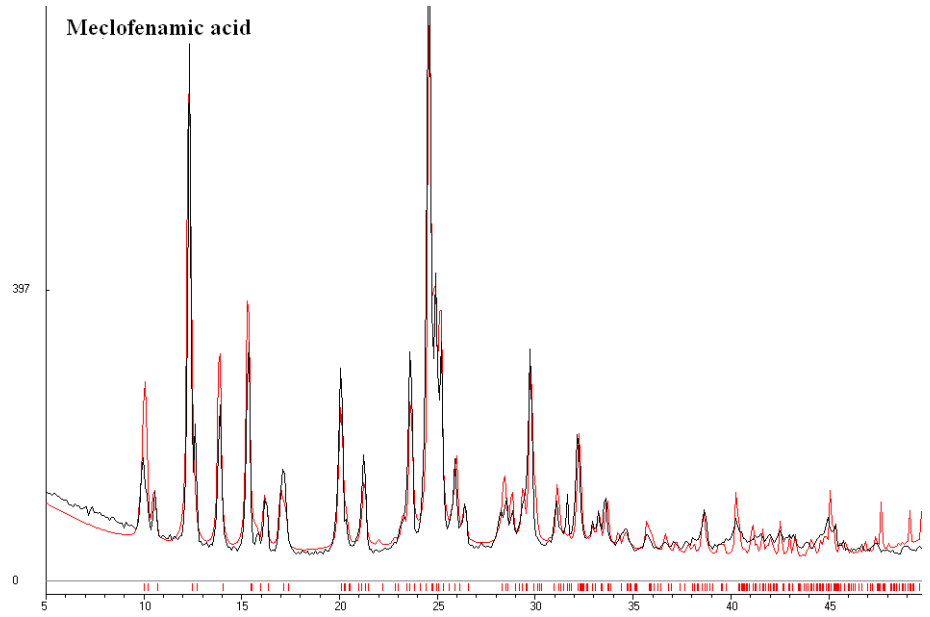


(a)

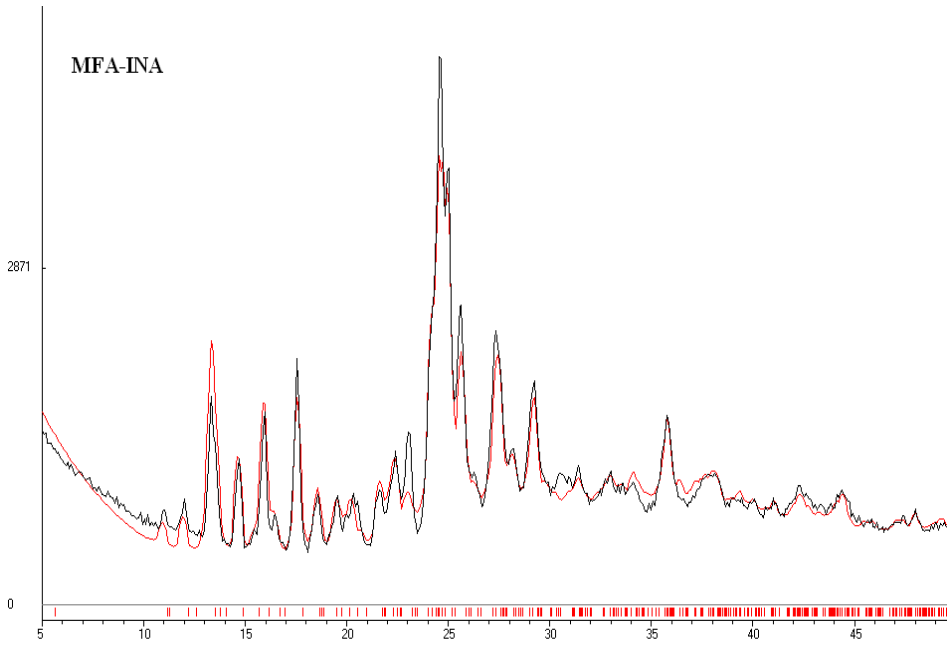


(b)

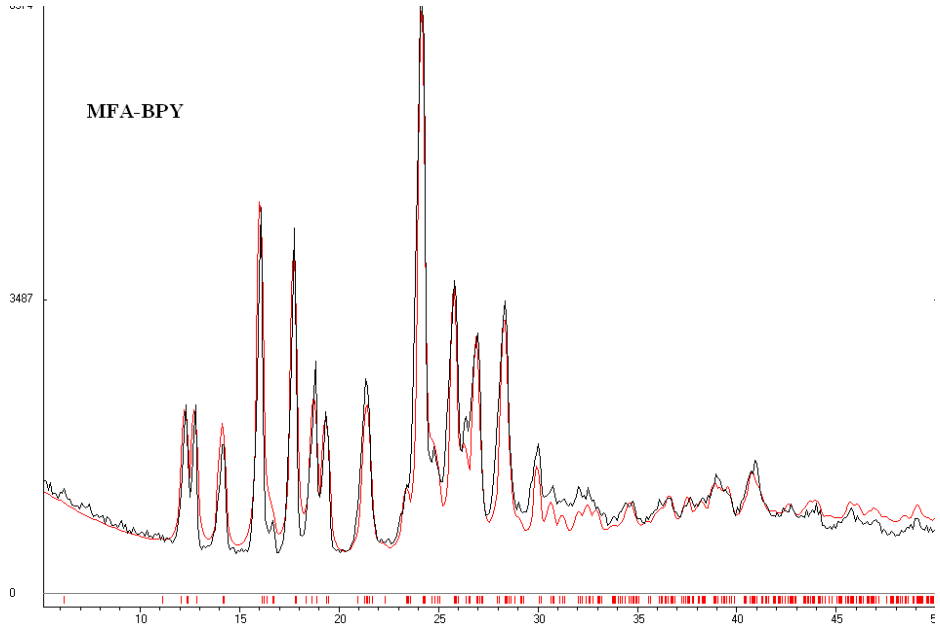
Figure S2 TGA of (a) piperazinium meclofenamate monohydrate (1:1:1) and (b) 4-aminopyridinium meclofenamate monohydrate (1:1:1) are consistent with one water stoichiometry.


Meclofenamic acid
397
0
5
10
15
20
25
30
35
40
45

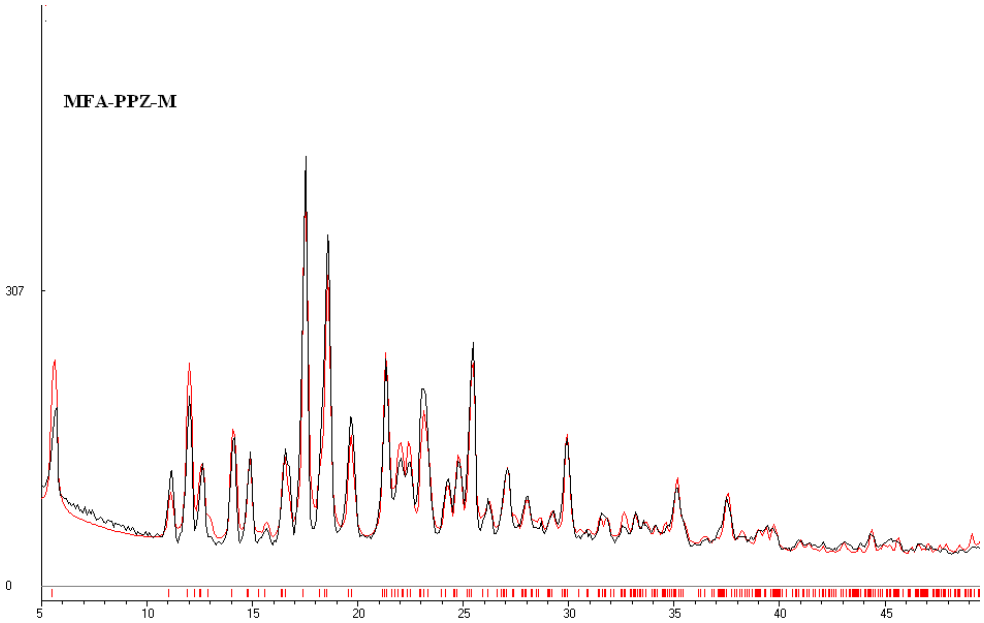
(a)


MFA-INA
2871
0
5
10
15
20
25
30
35
40
45

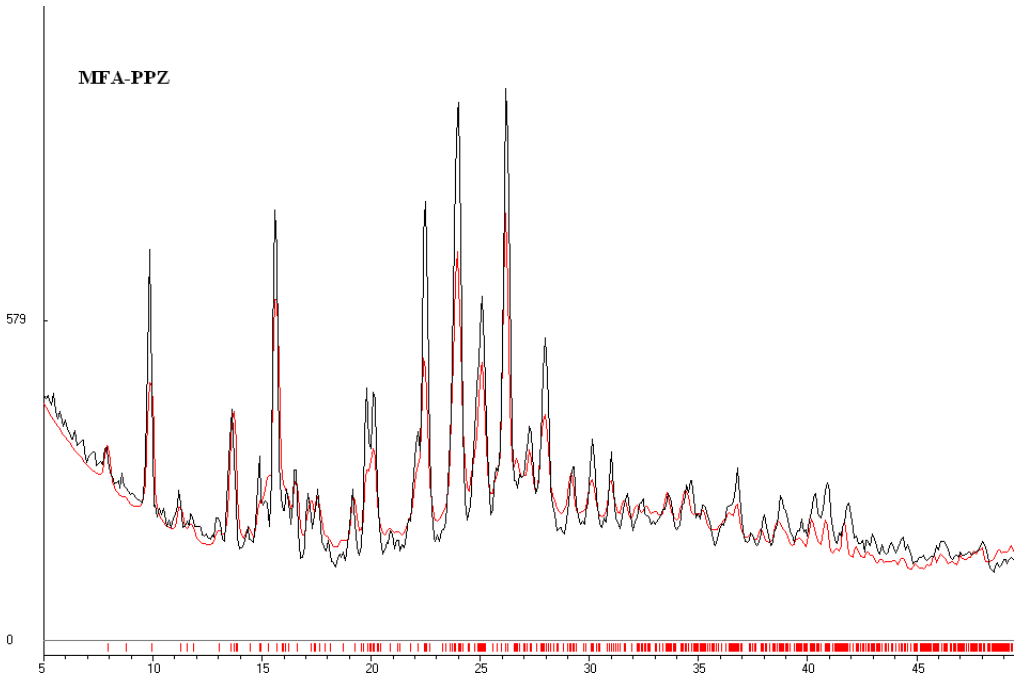
(b)


MFA-BPY
3487
0
10
15
20
25
30
35
40
45

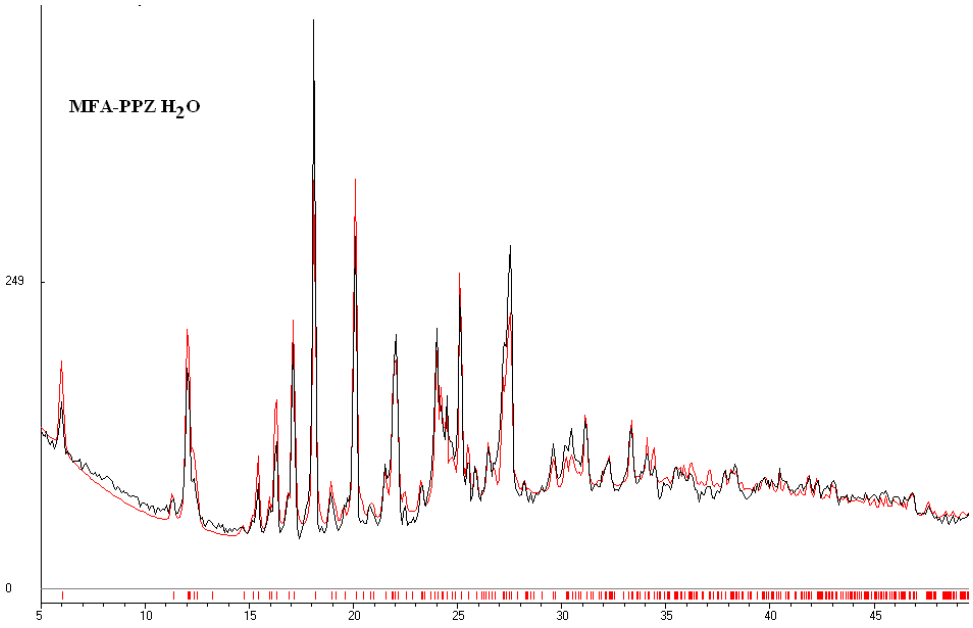
(c)


MFA-PPZ-M
307
0
5
10
15
20
25
30
35
40
45

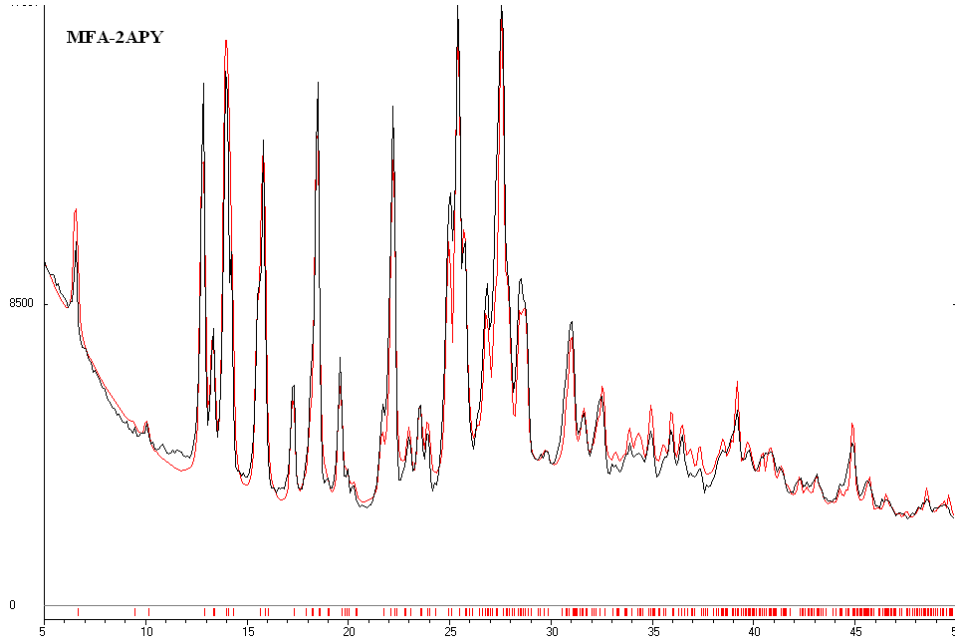
(d)


MFA-PPZ
579
0
5
10
15
20
25
30
35
40
45

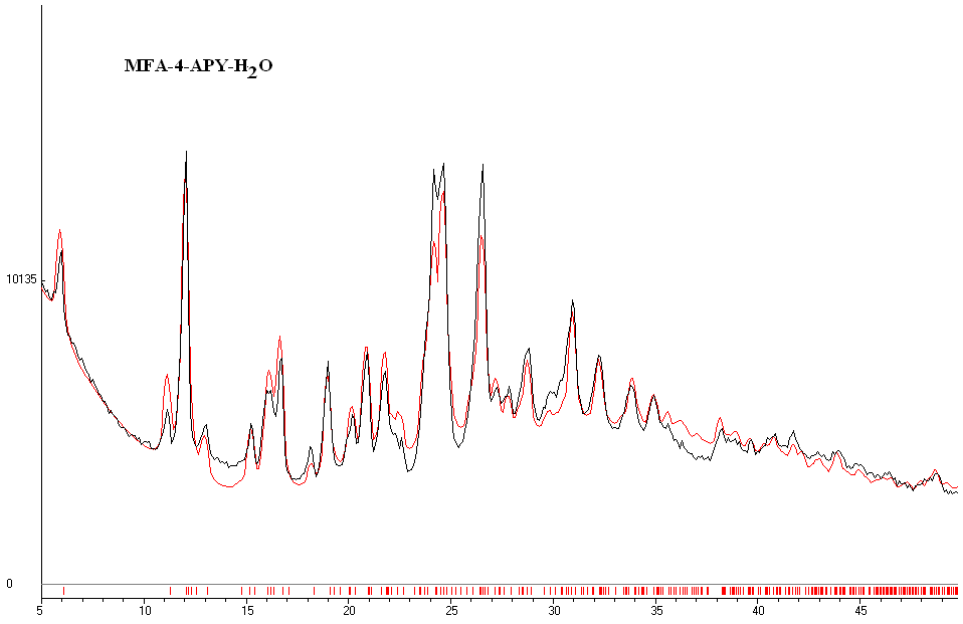
(e)


MFA-PPZ H2O
249
0
5
10
15
20
25
30
35
40
45

(f)



(g)



(h)

Figure S3 PXRD comparison of experimental pattern (black) with calculated lines from the X-ray crystal structure (red). (a) Meclofenamic acid, (b) meclofenamic acid–isonicotinamide, (c) meclofenamic acid–4,4'-bipyridine, (d) monoclinic polymorph of piperazinium meclofenamate salt (1:1), (e) piperazinium meclofenamate salt (2:1), (f) piperazinium meclofenamate salt monohydrate (1:1:1), (g) 2-aminopyridinium meclofenamate salt (1:1), and (h) 4-aminopyridinium meclofenamate salt monohydrate (1:1:1).

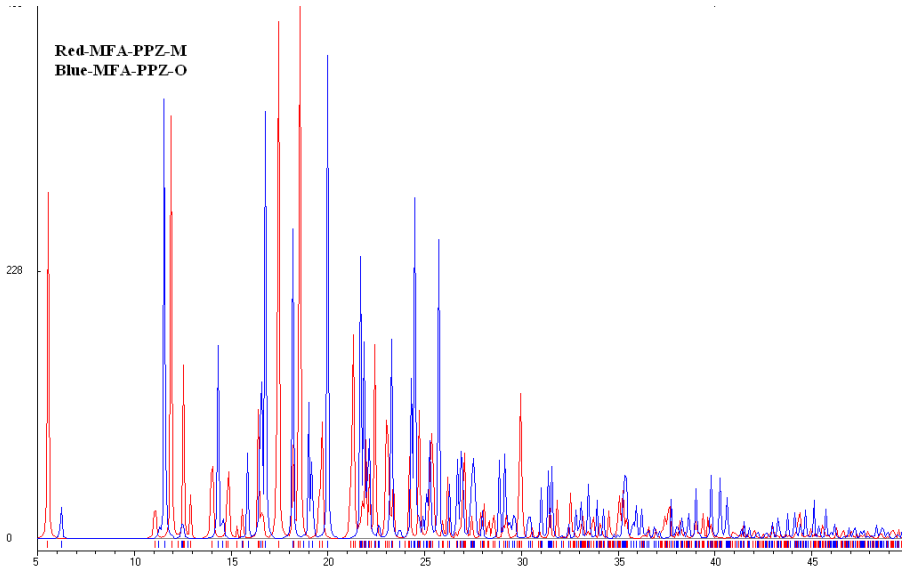
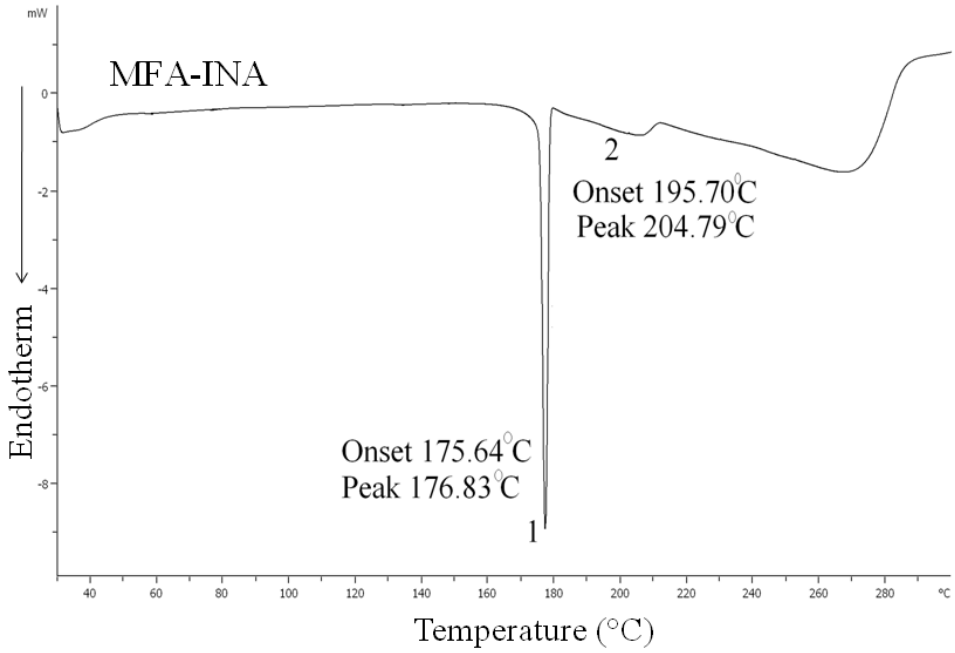
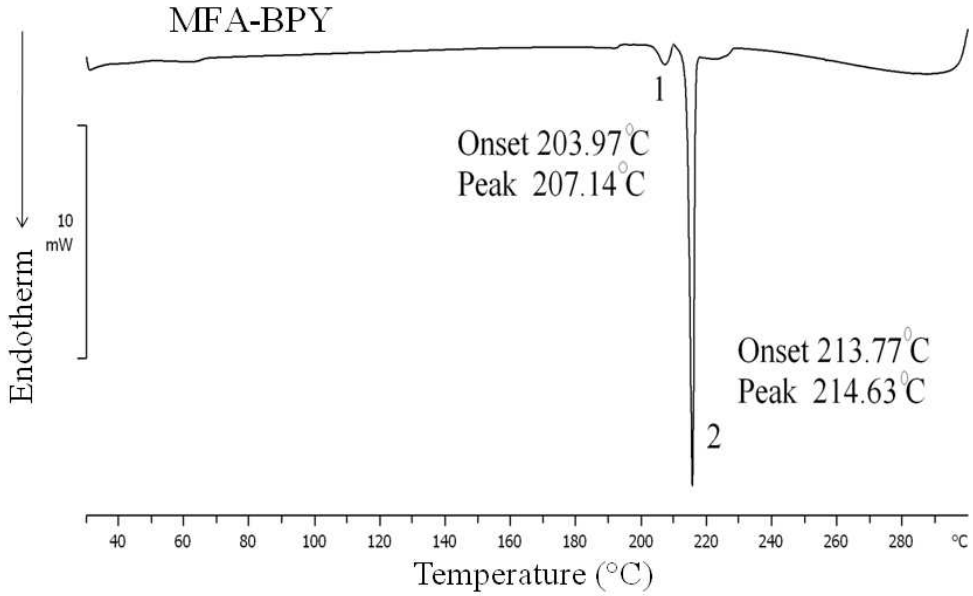


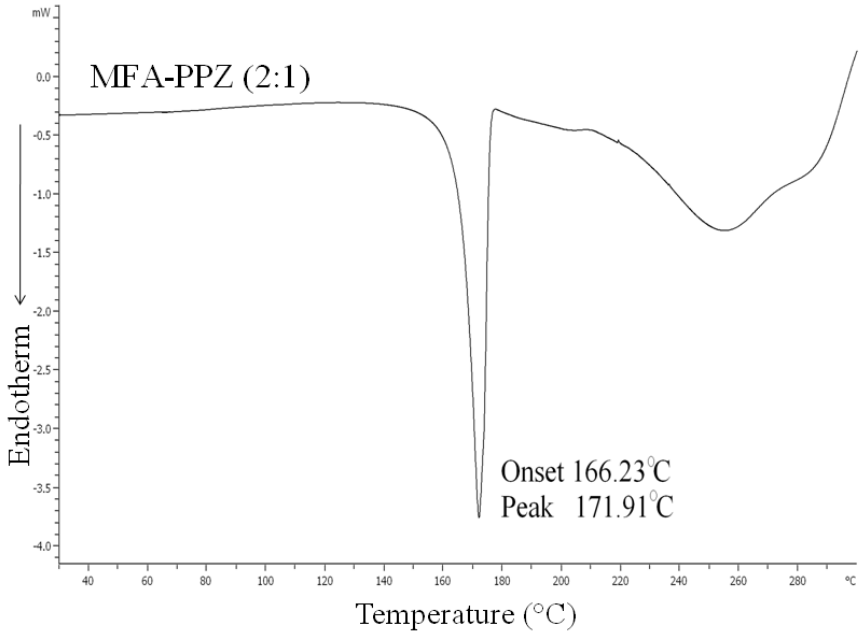
Figure S4 Comparison of calculated X-ray diffraction lines of monoclinic (red) and orthorhombic (blue) forms of piperazinium meclofenamate (1:1) salts.



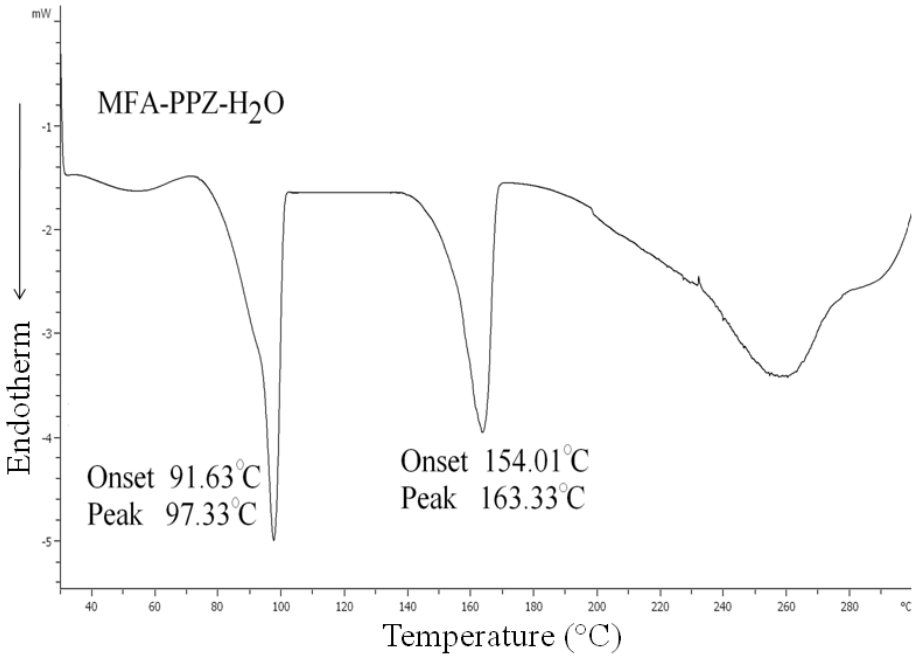
(a)


MFA-BPY
1
Onset 203.97°C
Peak 207.14°C
Endotherm
10
mW
Onset 213.77°C
Peak 214.63°C
2
40 60 80 100 120 140 160 180 200 220 240 260 280 °C
Temperature (°C)

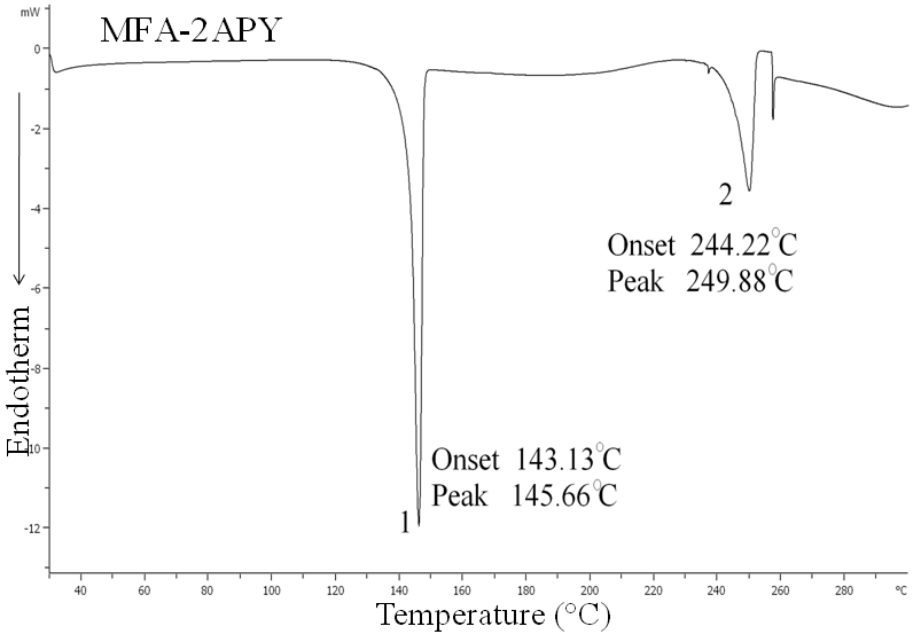
(b)


mW
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
MFA-PPZ (2:1)
Endotherm
Onset 166.23°C
Peak 171.91°C
40 60 80 100 120 140 160 180 200 220 240 260 280 °C
Temperature (°C)

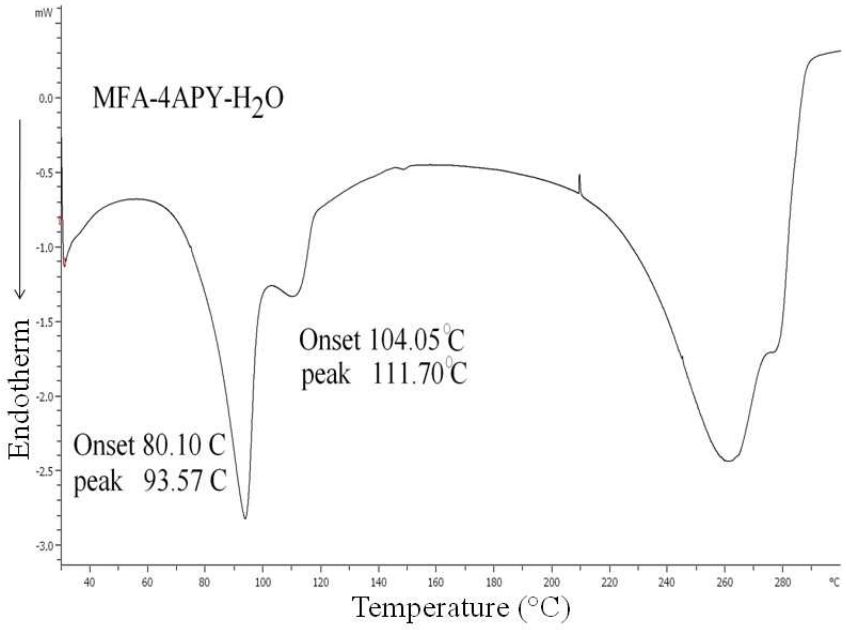
(c)


mW
MFA-PPZ-H2O
Endotherm
Onset 91.63°C
Peak 97.33°C
Onset 154.01°C
Peak 163.33°C
Temperature (°C)

(d)


mW
MFA-2APY
Endotherm
2
Onset 244.22°C
Peak 249.88°C
Onset 143.13°C
Peak 145.66°C
1
Temperature (°C)

(e)



(f)

Figure S5 DSC endotherm of (a) MFA−INA, (b) MFA−BPY, (c) MFA−PPZ (2:1), (d) MFA−PPZ−H_2O, (e) MFA−2-APY and (f) MFA−4-APY−H_2O. The broad endotherm at 240-260 °C corresponds to melting of meclofenamic acid (MFA m.p. 257-260 °C) which indicates that cocrystals/ salts/ hydrates dissociate to MFA upon heating.

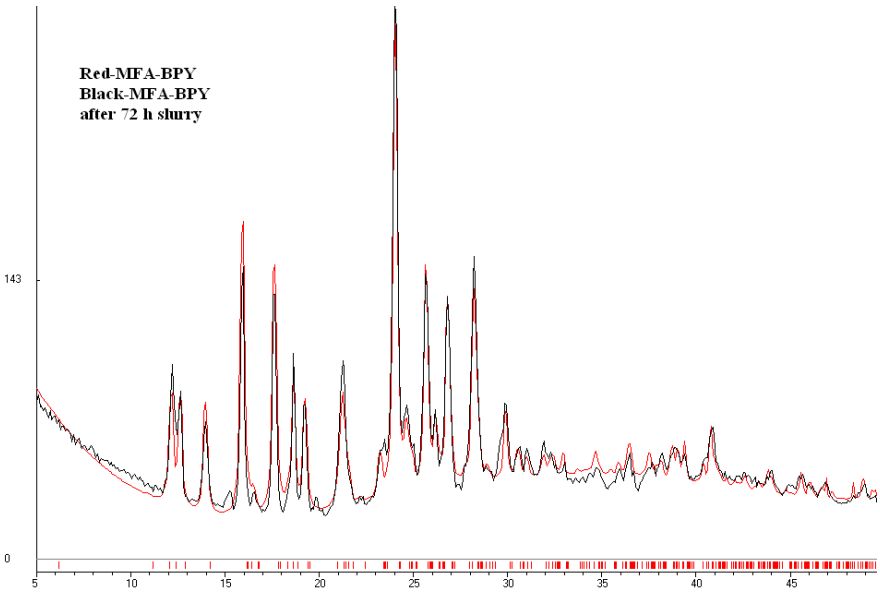


Figure S6 PXRD of meclofenamic acid–bipyridine cocrystal after 72 h slurry in 50% EtOH–water medium. The match of experimental pattern with that of the pure crystalline phase indicates the stability of this cocrystal in solution.

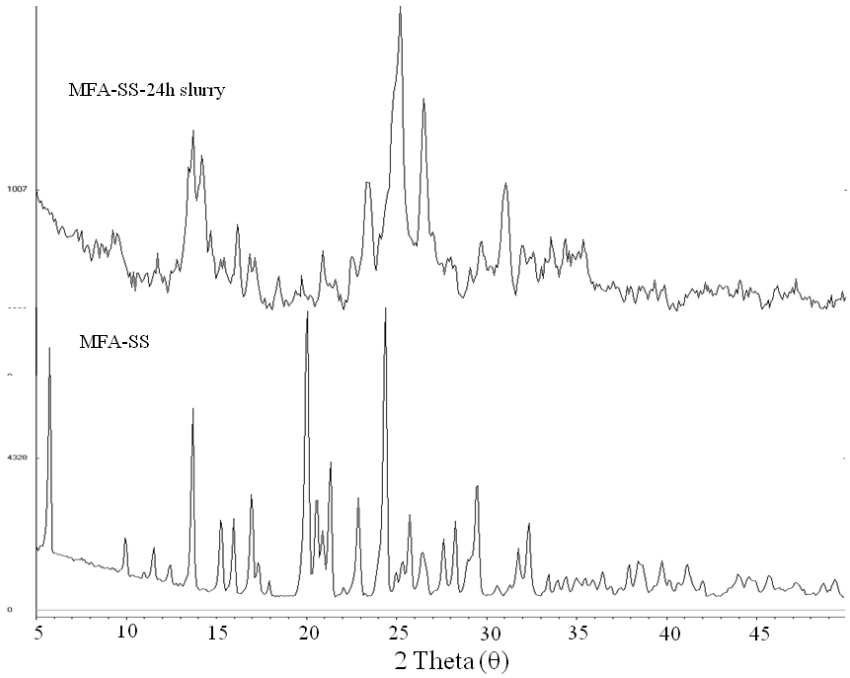


Figure S7 PXRD comparison of MFA−SS (Sigma-Aldrich) and after 24 h slurry in water medium indicates there is a possibility of hydrate form (see Figure S8).

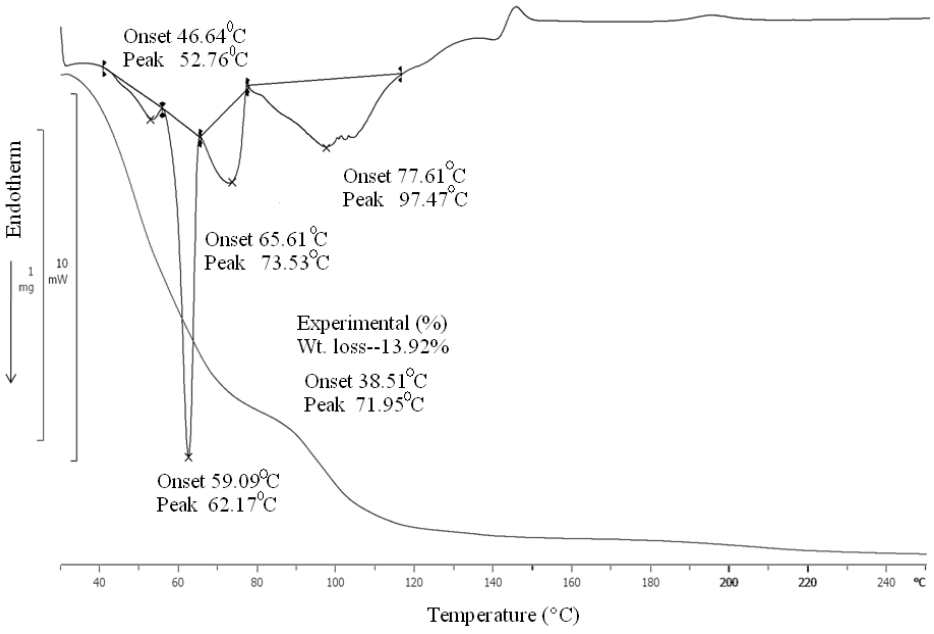


Figure S8 DSC and TGA thermograms of MFA−SS after slurry for 24 h in water indicates 2.8-2.9 equivalents of water content. The water content (13.85%) was confirmed by Karl-Fischer titration.